

Performance and prognosis in patients with lung cancer

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on behalf of the Edinburgh Lung Cancer Group*

Abstract

The Edinburgh Lung Cancer Group prospectively registered 651 new patients presenting with lung cancer during 1981; only 47 survived five years (7%). The survival rate was highest in patients selected for surgery (35/116, 30%) and in this group was related to cell type, stage of disease, and possibly to Karnofsky performance score (not statistically significant). By comparison with non-surgical patients these 116 patients undergoing surgery were highly selected in terms of age, favourable histological type, stage of disease, and performance score. Forty two of the 535 non-surgical patients were given radical radiotherapy alone and seven (17%) survived five years. The remaining 493 received palliative radiotherapy, chemotherapy (alone or combined with radiotherapy), or symptomatic treatment alone; only five (1%) survived five years. Median survival was related to cell type (adenocarcinoma 2.6 months, squamous cell carcinoma 6.2 months), stage (stage I 8.5 months, stage III 4 months), and Karnofsky performance index (≥ 90 9.3 months, ≤ 50 1.2 months). Age and sex had no independent prognostic value in any group. Performance score was highly correlated with stage (and age) and in this study represented the "best prognostic factor" in clinical practice.

Lung cancer presents a major problem in the United Kingdom with over 40 000 new cases each year.^{1,2} Survival is poor for all treatments except surgery. At the time of diagnosis about 80% of patients are unsuitable for surgical resection, usually because of the extent of their disease.³ If surgical resection is possible about 25% survive for five years, a proportion that has not changed appreciably over the last three decades.^{4,5} The major prognostic factors in patients undergoing surgical treatment include cell type, stage of disease, age, and absence of symptoms such as weight loss or pain.^{3,5,6} The outcome after surgical treatment may now be predicted with some confidence.⁶

Long term survival in patients with inoperable lung cancer is rare and only 2-3% survive five years despite chemotherapy or radical radiotherapy.^{7,8} Survival in individual patients with inoperable lung cancer may, however, vary from a few days to years, and predicting outcome remains difficult.⁹ Prognostic factors are now well defined for small cell carcinoma and include extent of disease, activity ("performance status") and the presence or absence of weight loss, bone pain, and liver metastases.^{10,11} Predicting outcome in non-small cell carcinoma remains more difficult.⁸⁻¹⁰

The activity or performance status of cancer patients was first assessed formally by Karnofsky and colleagues in 1949.¹² Various other performance scales have been developed, including those of the Eastern Cooperative Oncology Group (ECOG) and European Organisation for Research into the Treatment of Cancer (EORTC) systems.^{13,14} The Karnofsky performance score is now widely used by oncologists for patients with lung cancer but has been neglected by physicians dealing with non-small cell lung cancer, particularly in routine clinical practice as opposed to clinical trials.

Using the performance categories of "ambulatory" and "non-ambulatory" in patients with small cell and non-small cell lung cancer, Lagakos and colleagues found that these very simple criteria provided a more useful predictor of median survival than stage of disease or cell type.¹⁵

Members of the Edinburgh Lung Cancer Group see over 80% of all new patients presenting with lung cancer in South East Scotland.⁷ The Karnofsky performance score is prospectively recorded in all new patients with lung cancer registered by members of the group.

We have reviewed all new patients with lung cancer registered during the year 1981. Median and long term survival in patients with operable and inoperable disease have been related to various putative prognostic factors recorded prospectively, including performance status.

Methods

We reviewed all patients with newly diagnosed lung cancer registered by the Edinburgh Lung Cancer Group from January to December 1981. Details were entered prospectively on a standardised registration form, including age, sex, occupation, date of

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Unfavourable factors and risk scores for patients with lung cancer not treated surgically, according to Cox proportional hazards regression analysis

Risk factor	Risk score
Large cell carcinoma	+ 4
Stage III disease	+ 8
Karnofsky performance index:	
< 80	+ 8
< 60	+ 14

first symptoms and diagnosis, smoking history, body weight, results of investigations, and performance in terms of the Karnofsky index.¹² Disease staging using the TNM system¹⁴ was based on clinical and radiological features supplemented by the results of laboratory and other investigations. More than 80% of patients underwent bronchoscopy. In patients undergoing surgical resection staging included information from both preoperative findings and resected material. The diagnosis of lung cancer was based on positive histological or cytological appearances or, in the absence of a pathological specimen, on unequivocal clinical and radiological appearances. Most of the pathological reports were provided by the two pathologists in the group and their clinical colleagues using agreed criteria for the diagnosis of lung cancer based on a revised and updated version of the World Health Organisation classification.¹⁶ The treatment given to the individual patient was also recorded: surgery, palliative radiotherapy (18–30 Gy), radical radiotherapy (42–57 Gy),¹⁷ chemotherapy, or symptomatic treatment only.

Survival data were obtained from routine follow up of the patients, supplemented by information from the Cancer Registry for South East Scotland.¹⁸ Group differences

were tested by the χ^2 method. Actuarial survival in different sub-groups was compared by the life table method of Lee and Desu offered by the SPSSx program.¹⁹ Cox proportional hazards regression was used to test each prognostic factor while the remaining factors were controlled for, the BMDP program being used.²⁰ This is a form of multiple regression analysis, which permits risk modelling, whereby risk scores for different prognostic factors can be calculated and expressed in arbitrary units, the maximum risk score for an individual patient being 26. Preliminary analyses confirmed gross differences in survival between surgical and non-surgical patients and data on these two groups were consequently analysed separately.

Results

Six hundred and fifty one new patients with lung cancer were registered during 1981. Their mean age was 67 (range 29–91) years and 183 (28%) were female. The cell type was known in 547 cases (85%). Squamous cell carcinoma was the most common tumour (262, 48%) followed by small cell carcinoma (126, 23%), adenocarcinoma (66, 12%), large cell carcinoma (65, 12%), and other types of carcinoma (28, 5%). Cell typing was based on a biopsy specimen in 306 cases (56%), sputum (for cytological examination) in 126 (23%), a surgical specimen in 71 (13%), and material from other sources in 44 (8%). One hundred and sixteen patients (18%) were referred for surgical treatment, 78 (12%) for chemotherapy, 247 (38%) for symptomatic treatment only, and 233 (31%) for radiotherapy.

Seventy five (12%) of 651 patients registered in 1981 were alive two years after diagnosis, but only 47 (7%) after five years. The highest five year survival was 30% (35 of 116 patients) in those who were treated surgically. Eight of these 116 patients were found to have inoperable tumours at the time of surgery, and therefore underwent thoracotomy only (median survival 112 days).

PATIENTS TREATED BY SURGERY

The 116 surgical patients were a highly selected group. They were younger (24% v 39% aged over 70 years; $p < 0.01$) than the remaining 535 ("non-surgical") patients, had less advanced disease in terms of stage and TNM grading, were more likely to have a more favourable histological cell type, and were more active. The Karnofsky performance index was known in 591 patients. Seventy of the 79 surgical patients (89%) had a Karnofsky index of 80% or more, compared with only 240 of the 512 non-surgical patients (48%, $p < 0.01$ —fig 1). Five year survival rate after surgery was strongly associated with cell type, being 55% in patients with adenocarcinoma (11 of 20 patients), 31% in patients with squamous cell carcinoma (20/65) 12% in patients with large cell carcinoma (2/16), and 14% in patients with small cell carcinoma (1/7) ($p < 0.01$ —fig 2a). Other factors influencing long term survival were stage of disease (stage I + II, $n = 99$: five

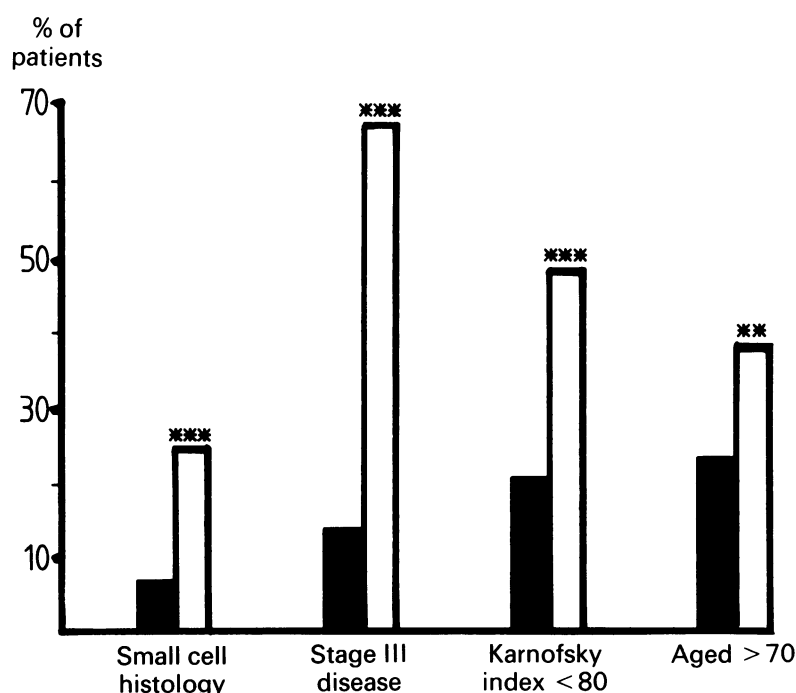


Figure 1 Comparison of the 116 surgical (■) and 535 non-surgical (□) patients: cell type, stage, performance index, and age. *** $p < 0.001$; ** $p < 0.005$.

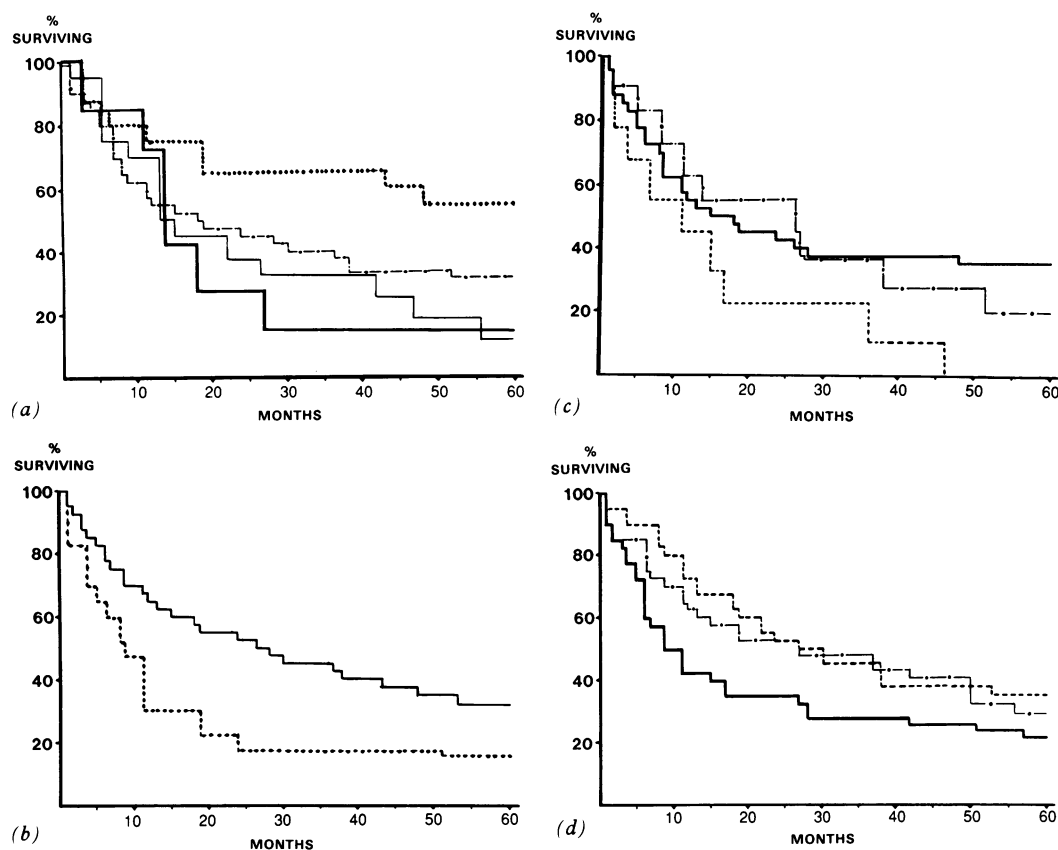


Figure 2 Five year survival in the 116 surgical patients according to: (a) cell type (.....20 adenocarcinoma; -----65 squamous carcinoma; —7 small cell carcinoma; —16 large cell carcinoma); (b) stage of disease (—99 stage I and II; -----17 stage III); (c) Karnofsky performance index (—60 patients with index 90–100; -----11 patients with index 80;9 patients with index 10–70); (d) age (—less than 60 years; -----60–69 years;over 70).

year survival 32%; stage III ($n = 17$): five year survival 19%; $p < 0.02$ —fig 2b). There was a trend towards an effect from the Karnofsky performance index (five year survival rate 36% in patients with a performance index of 90–100 (31 of 60 patients), 20% in patients with a performance index of 80 (4/20), and zero in nine patients with a performance index of 10–70 ($p = 0.08$ —fig 2c). Age had no independent prognostic value (fig 2d).

PATIENTS NOT TREATED BY SURGERY

Long term survival in the 535 patients not suitable for surgical treatment was poor; only 12 (2%) survived for five years. The overall median survival was 5.5 months.

Median survival in the 535 non-surgical patients was significantly related to cell type (adenocarcinoma 2.6 months, large cell carcinoma 3.4 months, small cell carcinoma 5.7 months, and squamous cell carcinoma 6.2 months; $p < 0.001$). It was also related to stage of disease (stage I median survival 8.5 months, stage II 11 months, stage III 4 months; $p < 0.001$) and Karnofsky performance index (median survival 9.3 months for performance index of 90 or more, 6.2 months for an index of 80, 4.5 months for an index of 60–70, and 1.2 months for an index of 50 or less; $p < 0.001$ —fig 3). Age had no independent prognostic value (median survival of 5.5, 6.5, and 4.5 months at ages below 60, 60–69, and 70 or more respectively).

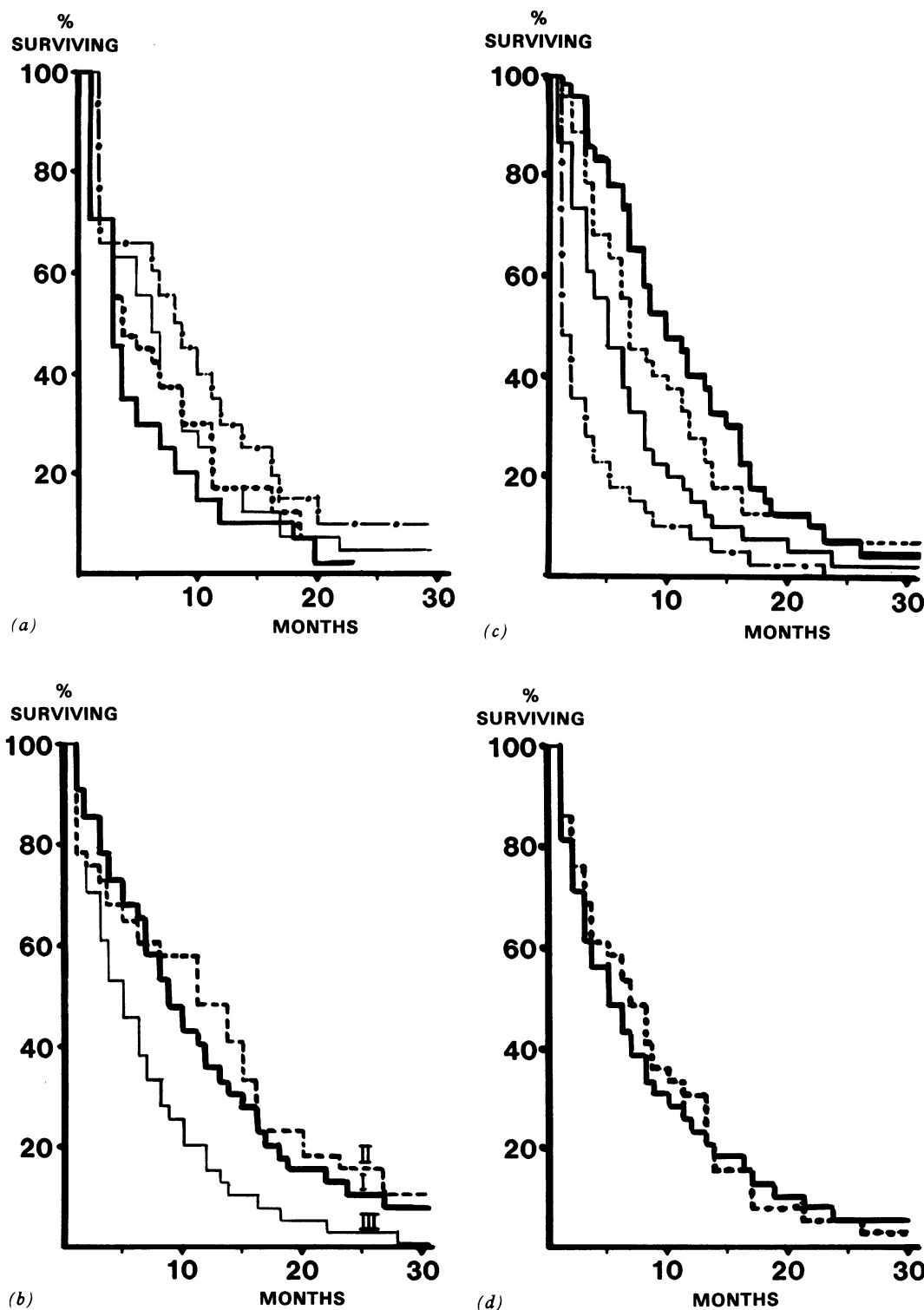
In the patients not treated with surgery the

Karnofsky performance index was weakly associated with stage of disease (Kendall rank correlation coefficient, $\tau = -0.19$, $p < 0.001$) and with age ($\tau = -0.20$, $p < 0.001$). The most important prognostic factors, according to the Cox proportional hazards regression, in order of ranking were Karnofsky performance index, stage of disease, and cell type. The table shows that a patient with large cell carcinoma, stage III disease, and a performance index below 60 has the maximum risk score. This same ranking was also apparent in the subgroups of patients with squamous carcinoma ($n = 241$) and in those undergoing palliative radiotherapy ($n = 192$): performance status $>$ stage $>$ cell type.

PATIENTS TREATED WITH RADIOTHERAPY

Two hundred and thirty three patients with non-small cell cancer received radiotherapy as primary treatment. Forty one (17%) received radical radiotherapy (42–57 Gy over four weeks) and 192 palliative radiotherapy (18–30 Gy over two weeks). Histological confirmation was available for 32 of the 41 patients undergoing radical radiotherapy and for 156 of the 192 patients undergoing palliative radiotherapy. The patients treated with radical radiotherapy differed from those receiving palliative radiotherapy in terms of stage (61% v 28% stage I; $p < 0.001$), age (76% v 57% under 70; $p < 0.03$), and performance (Karnofsky index over 80 in 79% v 49%; $p < 0.001$). Five year survival after radical radiotherapy was 17% (seven of 41 patients) overall,

Figure 3 Survival in the 535 non-surgical patients according to: (a) cell type (— 32 adenocarcinoma; —•— 206 squamous carcinoma; — 103 small cell carcinoma; —•••• 48 large cell carcinoma); (b) stage of disease (139 patients stage I, 32 stage II, 364 stage III); (c) Karnofsky performance index (— 104 patients with index 90–100; —•••• 126 patients with index 80; — 158 patients with index 60–70; —•— 99 patients with index <60); (d) age (— patients aged over 70; —•••• patients aged 60–69; the curve for patients aged under 60 overlay the other two and has been omitted).



including four of the 32 patients with histological evidence of carcinoma. Only three of 192 (1.5%) patients treated palliatively with radiotherapy survived five years.

Results of the patients with small cell carcinoma treated by chemotherapy have been reported elsewhere.²¹

Discussion

This study describes a large series of unselected patients with lung cancer. Previous work suggests that up to 83% of all patients with lung cancer in the catchment area of 950 000 are seen by members of the group.⁷ These data

therefore reflect routine clinical practice in South East Scotland and are probably representative of practice elsewhere in the United Kingdom.

The overall prognosis in lung cancer remains poor. Only 7% of the 651 patients diagnosed in 1981 remained alive five years later. The principal factor determining selection for surgical resection or radical radiotherapy was extent of disease; cell type, Karnofsky performance index, and age also influenced the decision. This basis for selecting patients is similar to that found in other series.^{8,22} Patient selection may create major problems when lung cancer series from different centres are compared. In a

review of two studies of patients with small cell carcinoma one was shown to have a median survival 5–15 weeks longer in all subgroups than the other. Although they were allegedly comparable in terms of study entry criteria, “strong but undetermined factors” were blamed for the differences in survival.¹⁰ Differences in selection of patients is a much more likely explanation and is likely to account for much of the variation in long term survival (4–20%) after very similar chemotherapy regimens for small cell carcinoma.^{23–25} Selection of patients with smaller, less advanced, and possibly slower growing primary tumours may obviously bias any assessment of prognostic factors or therapeutic interventions.²⁶ New treatments showing clear “promise” in early studies will therefore still require assessment in randomised controlled studies.¹⁰

In our series the outlook for patients undergoing surgical resection, a highly selected minority, was far better than in all other groups, 30% remaining alive at five years. We have confirmed that the principal prognostic factors in surgically treated patients are cell type^{6,27} and stage of disease.^{10,28} Although squamous carcinoma is usually considered to have the best prognosis,⁶ a survival advantage for adenocarcinoma similar to that seen in our study has been reported elsewhere in Europe^{29,30} and possibly the United States.²⁷ This may reflect the consistently slower rates of tumour growth observed with adenocarcinomas than with other cell types.^{26,31} Although our data suggested that the Karnofsky performance index might have some prognostic value in surgical patients, very few fell into the poor performance categories and the differences did not reach statistical significance. Other series of surgical patients suggest that the principal prognostic factors, in order of importance, are cell type, stage of disease and tumour size,^{32,33} pain, and weight loss, but not performance score.^{6,10,34,35} Concomitant cardiac and pulmonary disease other than the lung cancer may also decrease survival.³⁶ Age has had no prognostic value in this or other series,¹⁰ though some authors disagree.²⁷ Similarly, we found that female sex did not give survival benefit.^{27,37,38} With the use of regression equations the principal factors have been applied prospectively with good predictive value.⁶

In this study most patients not having surgery died within a year of diagnosis, and only 2% survived five years. The median survival was about six months, in accord with other series.^{39,40} Median survival was closely associated with the Karnofsky performance index and also with cell type and stage of disease, but not age. Staging of disease in 1981 was often fairly elementary, and few of these patients had computed tomography, for instance. The particularly poor median survival in our 32 patients with inoperable adenocarcinoma was unexpected and, although survival was similar in one American series,²⁷ contrasts with the figures in the larger series of Hyde.³⁹ Several other potential prognostic factors, taken in isolation, appear to have some value, including a raised erythrocyte sedimentation

rate and total white blood count,^{33,41} a reduced lymphocyte count, raised values in liver function tests^{10,33} (or other evidence of liver metastases¹⁰), weight loss,²⁴ anaemia, and bone pain.⁴² Biochemical and performance measures are particularly valuable in patients with small cell carcinoma.⁴³ Prognostic factors are often associated, as the performance index was with stage and age in this series. Some form of multiple regression analysis is therefore desirable to identify and rank the most valuable prognostic factors.⁴³ We found that the performance index was superior to both cell type and stage of disease in non-surgical patients. These prognostic factors remain significant, unlike age or sex, irrespective of treatment in patients with inoperable lung cancer.¹⁰

Although the value of a performance index in small cell carcinoma is now widely recognised,^{24,28,43} its value in non-small cell carcinoma has been reported infrequently, and mostly by American authors.¹⁰ Our study confirms activity as a major prognostic factor in patients with inoperable lung cancer.

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